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journal homepage: www.elsevier.com/locate/ijidInfections due to *Pseudallescheria/Scedosporium* species in patients with advanced HIV disease – a diagnostic and therapeutic challengeIna Tammer^{a,*}, Kathrin Tintelnot^b, Rüdiger C. Braun-Dullaeus^c, Christian Mawrin^d, Cordula Scherlach^e, Dirk Schlüter^a, Wolfgang König^a^a Institute of Medical Microbiology, Otto-von-Guericke University, Leipziger Str. 44, 39 120 Magdeburg, Germany^b Division of Mycology, Robert Koch Institute, Berlin, Germany^c Internal Medicine, Department of Cardiology, Angiology, and Pneumology, Otto-von-Guericke University, Magdeburg, Germany^d Institute of Neuropathology, Otto-von-Guericke University, Magdeburg, Germany^e Institute of Neuroradiology, Otto-von-Guericke University, Magdeburg, Germany

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SUMMARY

Objectives: The aim of this study is to highlight the importance of infections caused by members of the genera *Pseudallescheria/Scedosporium* in HIV-positive patients.**Methods:** We describe a case of a fatal scedosporiosis in a treatment-naïve HIV patient and review all previously reported cases of pseudallescheriosis/scedosporiosis from a search of the PubMed and Deutsches Institut für Medizinische Dokumentation und Information (DIMDI) databases, applying the terms 'Pseudallescheria', 'Scedosporium', 'Allescheria', 'Monosporium', 'Petriellidium', 'boydii', 'prolificans', 'inflatum', cross-referenced with 'HIV' and 'AIDS'.**Results:** Detection of *Scedosporium* and *Pseudallescheria* species has been reported in 22 HIV-positive patients. Fourteen isolates belonged to the *Pseudallescheria boydii* complex and eight to *Scedosporium prolificans*. Invasive scedosporiosis (IS) was proven in 54.5% of the patients. Among them dissemination was observed in 66.7%. *Pseudallescheria/Scedosporium* species were mainly isolated from male individuals. Patients with proven IS showed CD4+ cell counts <100/μl and a higher co-infection rate as compared to colonized patients. Patients with central nervous system (CNS) manifestations showed CD4+ cell counts <50/μl. The mortality rate for patients with proven IS was 75% and was 100% for patients with dissemination/CNS manifestations. The fatality rate for patients treated with antifungal drugs plus surgery was lower compared to patients treated with antimycotic agents alone.**Conclusions:** IS only occurred in HIV-positive patients with a strongly impaired immune system. The survival rates of patients with advanced HIV disease and invasive scedosporiosis can be improved by rapid diagnosis by biopsy and requires complex therapy with a combination of active antifungal drugs, surgery and supportive immune augmentation.

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1. Introduction

Opportunistic mould infections have been considered an infrequent complication of the HIV disease. Pulmonary aspergillosis, listed as an opportunistic infection in HIV-infected adults and adolescents by the Centers for Disease Control and Prevention (CDC), is the most frequently diagnosed clinical feature in this risk group.¹ Reports on diseases caused by other species such as zygomycetes and *Pseudallescheria/Scedosporium* species are rare. Nevertheless, in retrospective autopsy studies, a substantial number of fatal cases have been characterized following missed ante-mortem diagnosis.²

In this article, we present a case of a cerebral infection due to *Scedosporium apiospermum* in a patient with AIDS. Based on a literature review we highlight the importance of this fungal organism and related species, most frequently resistant to amphotericin B, as causes of life-threatening infections in individuals with advanced HIV disease.

2. Case report

A 31-year-old cachectic woman was admitted to a secondary hospital because of progressive neurological symptoms without further specification (June 2007). Based on these symptoms, a positive Toxoplasma antibody titer, and typical contrast-enhanced lesions on magnetic resonance imaging (MRI), cerebral toxoplasmosis was suggested. Toxoplasmosis, cachexia, and pharyngeal candidiasis were highly suggestive of an HIV infection, which was

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confirmed by an HIV-1 RNA level of 306 000 copies/ml and a CD4+ cell count of 31 cells/ μ l. Toxoplasma encephalitis (TE) was first treated with pyrimethamine, sulfadiazine, folic acid, and corticosteroids. Sulfadiazine was changed to clindamycin because of an allergic skin reaction. Further diagnoses were cytomegalovirus (CMV) reactivation diagnosed by CMV pp65 antigenemia, and herpes simplex virus (HSV) reactivation confirmed by positive PCR from blood samples. The HSV infection was treated with intravenous acyclovir therapy. Antiretroviral therapy (ART) was initiated with abacavir/lamivudine and ritonavir-boosted amprenavir. The *Candida albicans* pharyngitis was treated with fluconazole. The patient responded well to the therapy, resulting in a decrease in the neurological symptoms, a reduction in the cerebral foci, a decline in the HIV viral load to 117 copies/ml, and an increase in the CD4+ count to 150/ μ l. On day 53 after admission the patient was discharged from the hospital.

Three weeks later (day 74) the patient suffered from paresthesia, paresis of the left side, and reduced taste sensation. She tended to tilt but had no fever. At admission to the University Clinic Magdeburg the following parameters were apparent: C-reactive protein (CRP) 21.5 mg/l, leukocytes 12.9×10^9 /l, CD4+ cell count 16 cells/ μ l, HIV viral load negative. MRI showed multiple foci localized in the cerebrum, cerebellum, and in the basal ganglia concordant with TE (Figure 1). Neurological symptoms were considered as a side effect of the pyrimethamine therapy, resulting in a dose reduction to 100 mg/day. ART and antiparasitic therapy were continued as recommended. Clinical symptoms declined and the woman was again discharged from hospital after 6 days (day 79).

Three weeks later (day 94) the patient was re-admitted to the hospital in a poor general condition (days 94–114). A detailed examination showed paralysis of ocular movement, anisocoria, ataxia, and hyperreflexia of the right side. Laboratory findings showed a CD4+ cell count of 45/ μ l and an HIV viral load of 1120 copies/ml. The spinal fluid showed <5 cells/ μ l, an increased protein concentration of 746 mg/l (normal <450 mg/l), and a massive disturbance of the blood–brain barrier. PCR testing of the cerebrospinal fluid (CSF) targeting HSV1/2-, CMV-, and *Toxoplasma gondii*-specific genes, as well as screening tests for cryptococcal antigen were negative. MRI was unchanged.

Four weeks later (day 146) the patient became stuporous and had repeated convulsions. Her CD4+ count was 30/ μ l and HIV-1 RNA level was <40 copies/ml. Surprisingly, MRI revealed an

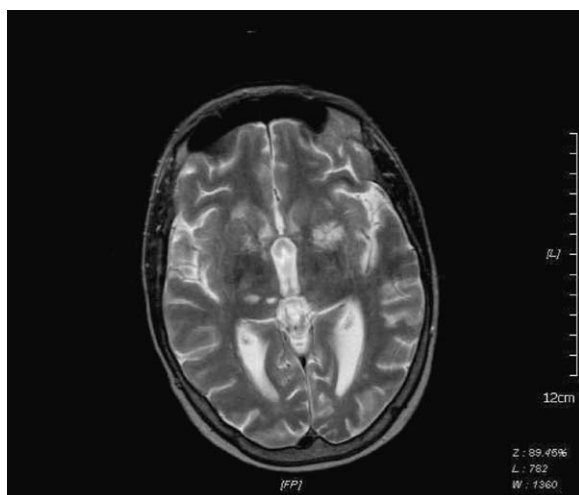


Figure 1. MRI at day 75 after first admission. T2 transverse scan (Siemens Magnetom Vision 1.5 T): multiple, rounded T2 hyperintense lesions on both sides of the basal ganglia, compatible with cerebral toxoplasmosis.

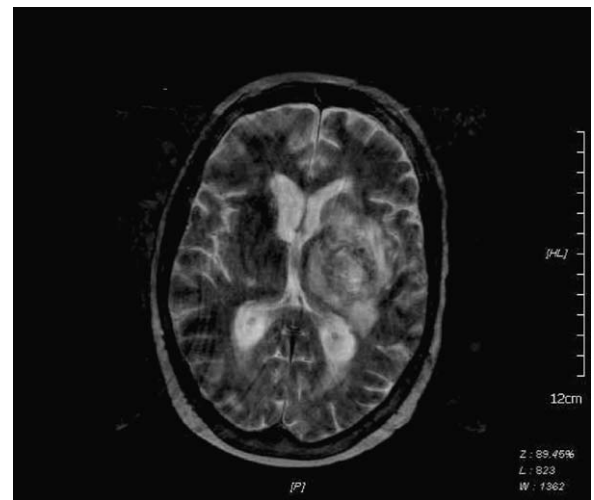


Figure 2. MRI at day 148 after first admission. T2 transverse scan (Siemens Magnetom Vision 1.5 T): new inhomogeneous, rounded mass of approximately 30 mm in diameter in the thalamus region and the left lateral basal ganglia with perifocal edema and compression of the left lateral ventricle.

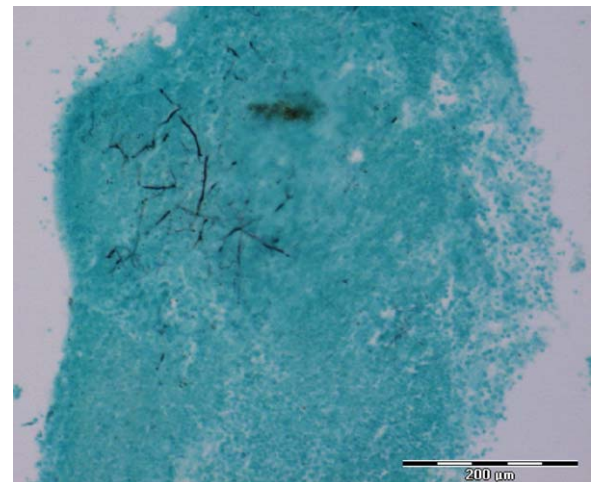


Figure 3. Histopathological examination. Necrotic and hemorrhagic brain tissue derived from a brain biopsy, with demonstration of fungal elements using Grocott's methenamine silver stain; magnification of $\times 200$.

additional mass measuring 4×4 cm in the right basal ganglia, surrounded by a pronounced focal edema with collapse of the ventricular system and a dislocation of the midline (Figure 2). A stereotactic biopsy was performed. Microscopic examination from the biopsy revealed tissue invasion (Figure 3) by branched, septated hyphae (Figure 4). Thus, a combined antifungal therapy with voriconazole and caspofungin was started. The course of disease was further complicated by multi-organ failure. The patient died on day 166. Permission for autopsy was denied.

2.1. Additional microbiological investigations

After 2 days of incubation at 37°C a hyphomycete was detectable from cultures of the brain biopsy on blood agar plates. Macro- and microscopic features allowed a primary classification to the *Pseudallescheria boydii* complex. Based on sequence analysis of the internal transcribed spacer (ITS) regions, the isolate was identified as *S. apiospermum*. In vitro susceptibility testing revealed minimum inhibitory concentrations (MICs) of $2 \mu\text{g/ml}$ for voriconazole and $>16 \mu\text{g/ml}$ for terbinafine, and a minimal

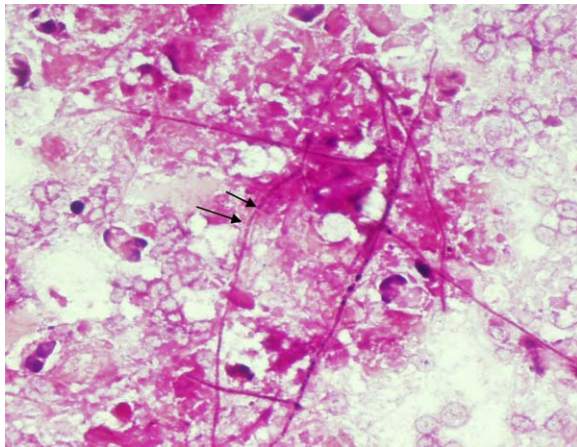


Figure 4. Microbiological examination of the cerebral tissue with Gram staining, showing branched septate hyphae (black arrows); magnification of $\times 200$.

effective concentration (MEC) of 0.5 $\mu\text{g/ml}$ for caspofungin after 48 h of incubation. The isolate was deposited in the strain collection of the Reference Laboratory of Mycology (Robert Koch Institut (RKI), Berlin, Germany) under the number RKI 07-0571. The sequence of the ITS regions was submitted to the NCBI database and is available under GenBank accession number **HQ857581**.

3. Methods

Because of several taxonomic changes we searched PubMed and the Deutsches Institut für Medizinische Dokumentation und Information (DIMDI) databases with the keywords:

'Pseudallescheria', 'Scedosporium', 'Allsheria', 'Monosporium', 'Petriellidium', 'boydii', 'prolificans', 'inflatum', cross-referenced with 'HIV' and 'AIDS' in order to identify published cases of *Pseudallescheria/Scedosporium* sp in HIV-infected persons.

A total of 24 additional cases, 22 in English and two in Spanish, were identified as dealing with these pathogens in HIV-infected people. The cases are listed in Table 1 in chronological order of the year of publication. It must be noted that cases 12 and 15 describe the same patient; this is also the case for cases 13 and 22. In addition, cases 23 and 24 most likely refer to the same patient. Hence these cases were summarized and counted as one case each. Thus, a total of 22 case reports (including the case presented here) were analyzed with regard to the following criteria: causative species, clinical symptoms, manifestations of the disease, complications, concomitant diseases, laboratory findings, treatment regime, and outcome, if available. Case 4 was only published as an abstract.

Invasive infections due to these pathogens are entitled 'invasive scedosporiosis' (IS). The cases were defined as 'proven' according to the definitions of the European Organization for Research and Treatment of Cancer/Invasive Fungal Infections Cooperative Group and the National Institute of Allergy and Infectious Diseases Mycoses Study Group (EORTC/MSG) consensus group.³ Patients without signs and symptoms of clinical disease were categorized as colonized, including those with fungus ball formation in pre-existing cavities without demonstration of fungal elements in diseased tissue.

The co-infection rate was calculated from the number of diseases per case.

Based on new morphological, physiological, and molecular data, the taxonomy of the fungi belonging to the genera *Pseudallescheria* and *Scedosporium* has been revised in recent years. *P. boydii* and *S. apiospermum* are now described as two

distinct species grouped into the newly defined *P. boydii* complex.^{4,5} *Scedosporium prolificans*, formerly *Scedosporium inflatum*, is distantly related to the *P. boydii* complex.

4. Results

Detection of *Scedosporium* and *Pseudallescheria* species has been reported in 22 HIV-positive patients (Table 1).^{6–27} Fourteen isolates belonged to the *P. boydii* complex and eight to *S. prolificans*.

The most frequent portal of mould entry was the respiratory tract (68.2%). In 86.7% of these cases the moulds were present in the lung and in 13.3% in the paranasal sinuses. Three of the 22 patients (13.6%) suffered from otitis externa, whereas in four patients (18.2%) the portal of entry remained unclear.

Invasive scedosporiosis was proven in 12 of the 22 patients (proven IS; 54.5%). Ten patients met the criteria of 'colonization', including three patients harboring a fungus ball in pulmonary cavities. One patient with fungus ball formation developed localized invasive infection, which was proven by histology. One patient was co-colonized with two species, *S. apiospermum* and *S. prolificans*.

Proven invasive fungal infection was caused by members of the *P. boydii* complex in eight patients and by *S. prolificans* in four patients.

IS was disseminated in eight of the 12 cases and was proven by either fungemia or autopsy (66.7%). Five of these patients developed central nervous system (CNS) manifestations.

Patients suffering from proven IS had 3.6 opportunistic diseases per case, whereas patients who were only colonized showed a co-infection rate of 2.0 on average (Table 2). Reactivation of members of the family *Herpesviridae* and candidiasis were the most frequently reported opportunistic infections. These were more frequent in patients developing disseminated rather than localized infections.

Co-isolation or infections due to *Aspergillus* species and *Pseudomonas aeruginosa* infections were exclusively observed in patients with proven IS.

The clinical outcome of the patients was fatal in 14 out of the 22 cases (63.6%, Table 1). Nine of all reported patients died as a result of their fungal disease, leading to a mortality rate of 40.9% (Table 3).

Among the patients with proven IS, 75% ($n = 9/12$) died, whereas 25% of the patients responded to therapy and survived ($n = 3/12$). In one of these cases the cause of death remains unknown. All survivors had localized infections caused by members of the *P. boydii* complex. In contrast, all patients suffering from proven *S. prolificans* infections died.

CD4⁺ cell counts were available for 15 of the 22 patients (Table 2). Ten of the 15 patients had cell counts $< 50/\mu\text{l}$ (66.7%). In addition, CD4⁺ counts $< 50/\mu\text{l}$ were reported from 62.5% of the patients with proven IS and from 71.4% of the colonized patients. The mean CD4⁺ cell count of the colonized patients was about three times higher than that of patients with proven IS. All patients with CNS manifestations showed CD4⁺ cell counts $< 50/\mu\text{l}$.

The HIV viral load was reported in seven of 22 patients (31.8%). Two of them were colonized and five patients suffered from proven IS. Patients with proven localized infections had a ca. two-fold higher viral load than colonized patients. Significant data about ART onset and virus resistances were not available.

ART was reported in detail in seven of 17 cases (41.2%) with previously known HIV infection (Table 4). Five patients were ART-naïve because pseudallescheriosis/scedosporiosis was the first manifestation of the AIDS disease. Two of them died before ART could be administered. No data were available for 10 cases.

Altogether seven of the cases were published in the era before highly active antiretroviral therapy (HAART) was introduced. Four

Table 1
Pseudallescheria/Scedosporium infection in patients with HIV/AIDS: clinical characteristics

Case No.	Ref.	Pathogen	Sex/age (years)	Location and/or diagnosis	Complications	Culture specimen that yielded moulds	Status of fungal infection	Outcome
1	Raffanti ⁶	<i>P. boydii</i>	M/53	Brain abscesses Mitral valve endocarditis	Dissemination, multiple cerebral emboli, coma, respiratory failure	Blood cultures Autopsy: mitral valve, CNS	Proven	Death
2	Scherr ⁷	<i>P. boydii</i>	M/44	Lung	Dissemination	Transbronchial biopsy, BAL Autopsy: kidney, lung	Proven	Death
3	Wood ⁸	<i>S. prolificans</i>	M/50	Lung		Sputum, BAL	Colonization	Survival
4	Garland ⁹	<i>S. apiospermum</i> <i>S. prolificans</i>	M/31	Left forearm Lung abscess	Dissemination	Biopsy of the nodule, lung abscess, heart, left forearm Autopsy: lung, kidneys, brain	Proven	Death
5	Meyer ¹⁰	<i>P. boydii</i>	M/44	Ethmoid/ sphenoid sinuses	Destruction of the right maxillary bone, respiratory failure	Aspirate	Colonization	Death of respiratory failure
6	Hopwood ¹¹	<i>S. prolificans</i>	M/44	Lung		Sputum, BAL	Colonization	Survival
7	Nenoff ¹²	<i>S. prolificans</i>	M/60	Lung	Dissemination	Autopsy: lung, kidney, spleen, CNS, myocardium	Proven	Death
8	Busaba ¹³	<i>P. boydii</i>	M/44	External auditory canal	Osteomyelitis of temporal bone, mastoiditis	Biopsy	Proven	Survival; latest follow-up visit 2 month later
9	Montero ¹⁴	<i>P. boydii</i>	M/33	CNS Brain abscesses	CNS: basal ganglia, pons, subependymal	Autopsy: CSF, brain tissue	Proven	Death after 6 days
10	Gonzalez ¹⁵	<i>S. prolificans</i>	M/43	Fungemia		Blood	Proven	Death
11	Horton ¹⁶	<i>P. boydii</i>	M/44	Sphenoid sinus Sinusitis	Epidural empyema of unknown origin	Necrotic debris of the sinus	Colonization	Death of unknown causes, most likely after non-proven fungal infection
12	Eckburg ¹⁷	<i>S. apiospermum</i>	M/21	Ear Mastoiditis	Pulmonary disease	Biopsy	Proven	Death by worsening pulmonary disease
13	Slack ¹⁸	<i>S. apiospermum</i>	M/10	Ear Otitis media	Pansinusitis, mastoiditis	Biopsy granuloma external ear canal	Proven	Survival
14	Rollot ¹⁹	<i>S. apiospermum</i>	F/29	Lung (fungus ball)		Lung tissue	Colonization	NR
15 (see case No. 12)	Yao ²⁰	<i>S. apiospermum</i>	M/21	Ear Otitis externa	Sinusitis, mastoiditis, pneumonia	Granulation tissue from mastoid, nasal cavity	Proven	Death probably to AIDS
16	Idigoras ²¹ (case 3)	<i>S. prolificans</i>	M/28	Disseminated infection	Dissemination	Blood, sputum, BAL, urine, feces (together with <i>Aspergillus fumigatus</i>) One sputum sample	Proven	Death 3 months later
17	Idigoras ²¹ (case 9)	<i>S. prolificans</i>	M/30	Lung			Colonization	Death
18	Idigoras ²¹ (case 10)	<i>S. prolificans</i>	M/34	Lung		Bronchial aspirate (repeated); BAL (together with <i>Aspergillus fumigatus</i>)	Colonization	Death 6 months later due to multifocal leuko-encephalopathy
19	Del Palacio ²²	<i>S. prolificans</i>	M/35	Lung	Cholecystitis	BAL, induced sputum (together with <i>Pseudomonas aeruginosa</i>)	Colonization	Death after progressive abdominal infection
20	Zaas ²³	<i>S. apiospermum</i>	M/42	Lung (fungus ball)		BAL	Colonization	NR
21	Garcia ²⁴	<i>P. boydii</i>	F/43	Lung (fungus ball)		Transbronchial biopsy	Colonization	Survival
22 (see case No. 13)	Abzug ²⁵	<i>S. apiospermum</i>	M/10	Ear Otitis media	Bone destruction of mastoid	Granuloma external ear canal	Proven	Survival
23	Mazumder ²⁶	<i>S. apiospermum</i>	F/31	Lung (fungus balls in multiple cavities)	Pneumothorax	Transbronchial biopsy lung tissue	Proven	Survival
24 (see case No. 23)	Sarva ²⁷	<i>S. apiospermum</i>	F/31	Lung (fungus ball)	Pneumothorax, left side	Tissue left lower lobe	Proven	Survival
25	Tammer (current case)	<i>S. apiospermum</i>	F/31	Multiple cerebral abscesses	Multiple cerebral lesions, pneumonia	Brain biopsy	Proven	Death

BAL, bronchoalveolar lavage; CNS, central nervous system; CSF, cerebrospinal fluid; NR, not reported.

Table 2
Laboratory findings and concomitant diseases

Variable	Colonization (n = 10/22)	Proven IS (n = 12/22)	
		Dissemination/CNS infection (n = 8/12)	Localized infection (n = 4/12)
CD4+ cell count (cells/μl)			
Available data (n)	7/10	4/8	4/4
<50	5	3	2
50–100	0	1	2
100–250	1	0	0
>250	1	0	0
Mean	118	38	34
HIV viral load (mRNA copies/ml)			
Available data (n)	2/10	2/8	3/4
<40	0	1	0
>40	2	1	3
Median	32 940	6 020	108 680
White blood cell count ($\times 10^9$/l)			
Available data (n)	2/10	3/8	2/4
Leukocytosis ($>12.0 \times 10^9$ /l)	0	1	1
Leukopenia ($<4.5 \times 10^9$ /l)	1	2	1
Normal value	1	0	0
Mean ($\times 10^9$ /l)	3.9	6.2	10.0
Neutrophil cell count ($\times 10^9$/l)			
Available data (n)	4/10	2/8	1/4
<0.5	1	0	0
>0.5	3	2	1
Mean	1.53	2.75	-
AIDS-related diseases			
Kaposi's sarcoma/lymphoma	2	3	0
<i>Pneumocystis jirovecii</i> pneumonia	3	2	2
<i>Herpesviridae</i> reactivation ^a	3	6	1
<i>Mycobacterium sp</i> ^b	2	0	2
Cryptococcal disease	0	0	1
Candida infection/colonization	3	4	1
Aspergillus infection/colonization	0	1	2
Toxoplasma encephalitis	0	1	1
Bacterial infection	2	2	3
Chronic hepatitis B/C	5	1	3
Co-infection rate (subgroups)	2.0	2.0	1.6

IS, invasive scedosporiosis; CNS, central nervous system.

^a *Herpesviridae* = cytomegalovirus, herpes simplex virus type 1/2, varicella zoster virus.^b *Mycobacterium sp* = *M. tuberculosis*, *M. avium-intracellulare*.

of them suffered from proven IS, three patients were colonized. In three of the cases with a proven IS fungal infection was the first manifestation of the HIV disease. All patients with proven IS died.

Fifteen cases were reported since the introduction of HAART. Among them were eight patients with proven IS and seven patients who were colonized. For two patients the detection of *Pseudallescheria/Scedosporium sp* guided to the diagnosis of AIDS. Of the eight patients with proven IS, three responded to therapy.

Antifungal treatment regimes (Table 4) were administered to nine of the 12 AIDS patients suffering from proven IS owing to the isolation of *Pseudallescheria/Scedosporium* species from a clinical specimen (75%). Five of these patients were treated with antifungal

agents alone and four underwent surgery in addition to antimycotic therapy. No patient was treated with surgery alone. Three patients died before antifungal treatment could be started.

Granulocyte colony-stimulating factor (G-CSF) was administered in three cases, and granulocyte macrophage colony-stimulating factor (GM-CSF) and interferon-gamma (IFN- γ) were administered in one case each (Table 4).

5. Discussion

Invasive or disseminated infections due to the genera *Pseudallescheria/Scedosporium* have been reported in immunocompetent and in immunocompromised patients.^{28–32} HIV infection per se has not been considered a major risk factor for mould infection, because the innate host defense is impaired only in the late stage of AIDS disease. Risk factors associated with the identification of *Aspergillus sp* in respiratory specimens from HIV-seropositive individuals have been found to be neutropenia, a CD4+ count <30 cells/ μ l, corticosteroid use, and *Pneumocystis jirovecii* infection.³³ Since members of the *P. boydii* complex and *S. prolificans* show virulence and clinical spectra similar to those of *Aspergillus* species, similar risk factors could be suggested.³⁴ At the time point of diagnosis of IS in our patient, her CD4+ cell count was <30 / μ l and the treatment regime of TE included corticoids. Reviewing the published cases, CD4+ counts <50 / μ l did not differ significantly between colonized and infected individuals. Nevertheless, patients with proven IS showed lower mean CD4+ cell

Table 3
Antifungal treatment and clinical outcome

Antifungal treatment regime	Antifungal drugs alone	Antifungal drugs + surgery	No antifungal treatment
Colonization (n = 10)			
Fatal outcome	1	0	0
Survivor	1	1	1
Other cause of death	1	2	1
Outcome not recorded	1	1	0
Proven IS (n = 12)			
Fatal outcome	4	1	3
Survivor	1	2	0
Other cause of death	0	1	0

IS, invasive scedosporiosis.

Table 4

Treatment regimes (available data)

Treatment regime	Colonization (n = 10/22)	Proven IS (n = 12/22)	
		Dissemination/ CNS infection (n = 8/12)	Localized infection (n = 4/12)
Antifungal treatment			
Antifungal drugs alone	4	4	1
Antifungal drugs + surgery	4	1	3
Surgery alone	0	0	0
No antifungal treatment	2	3	0
Immune augmentation			
G-CSF	1	1	1
GM-CSF	0	0	1
Interferon-γ	0	0	1
Antiretroviral therapy	2	2	3
Immunosuppressive therapy			
Corticosteroids	1	3	1
Additional therapy			
Antibiotic	4	5	4
Antiviral	4	2	0
Antiparasitic (<i>Toxoplasma</i> , PjP)	0	5	0
Prophylaxis			
Anti-Toxoplasma/PjP	3	0	1
Antifungal (fluconazole)	3	1	1

IS, invasive scedosporiosis; CNS, central nervous system; G-CSF, granulocyte colony stimulating factor; GM-CSF, granulocyte macrophage colony stimulating factor; PjP, *Pneumocystis jirovecii* pneumonia.

counts and a higher co-infection rate as compared to patients only colonized by *Pseudallescheria/Scedosporium* species.

Corticosteroids have a profound effect on the distribution and function of neutrophils, monocytes, and lymphocytes and are therefore reported to be associated with an increased risk of invasive aspergillosis in allogeneic hematopoietic stem cell transplant (HSCT) recipients.³⁵ In addition, *in vitro* investigations have shown that corticosteroids directly stimulate the growth of *Aspergillus fumigatus*, an effect not demonstrated for *Pseudallescheria/Scedosporium* species so far.³⁶ Previous corticosteroid treatment did not seem to influence the acquisition of *Pseudallescheria/Scedosporium sp* as it was administered in only four of the 12 patients with subsequent development of proven IS. Fluconazole prophylaxis given after cryptococcal disease did not prevent other mould infections like IS because fluconazole is ineffective against *Pseudallescheria/Scedosporium* species.

Analysis of the cases regarding the gender distribution showed a marked preponderance of males over females, resulting in a male/female ratio of 5:1 for patients with proven IS. Interestingly, Mylonakis et al.,³⁷ who analyzed 342 cases of pulmonary aspergillosis in AIDS patients, observed a male/female ratio of 4.9:1. As the gender distribution of HIV disease in Europe and Northern America is approximately 3:1,³⁸ a predisposition for the male is suggested.

Members of the *P. boydii* complex are ubiquitously distributed in soil and water, whereas *S. prolificans* is primarily isolated from soil and plants.³⁹ Furthermore, *S. prolificans* is geographically more restricted than members of the *P. boydii* complex. Thus, members of the *P. boydii* complex were more common in patients with advanced HIV disease as compared to *S. prolificans*. The origin of the patients colonized or infected by *S. prolificans* correlates with known endemic areas in the northern part of the Iberian Peninsula, Australia and the USA.^{22,40} Infections have rarely been reported from other countries.^{41,42}

Filamentous fungi enter the respiratory tract via inhalation; the skin, wounds, and eyes are infected by direct inoculation.⁴³ The respiratory tract, including the lung, was the most frequently reported portal of entry for *Pseudallescheria/Scedosporium sp* in patients with advanced HIV disease. Interestingly, members of the

P. boydii complex infected the host either via the respiratory tract or the external auditory canal, whereas *S. prolificans* exclusively infected the lung. In our patient, the mode of entry remains unclear. Small foci can be unapparent during the initial stages of the infection and may not be detected by radiographic means.⁴⁴ Similar observations have been described by Nenoff et al.,¹² as chest radiographs revealed no signs of pulmonary infiltration, but autopsy showed mycotic infiltrates in the left upper lobe of the lung.

In persons exposed to a high environmental inoculum of spores and with underlying pulmonary diseases, transient airway colonization may become persistent. Colonization of the respiratory tract due to *S. apiospermum* and *S. prolificans* was extensively evaluated in cystic fibrosis patients and in liver transplant recipients.^{22,45} Our review shows that colonization of the airway tract is not a rare event in AIDS patients. Interestingly, fungus ball formation in AIDS patients was exclusively caused by members of the *P. boydii* complex, although the lack of cases with fungus ball formations by *S. prolificans* may be due to the limited number of case reports. Nevertheless, in contrast to *Aspergillus* species, the role of members of the *P. boydii* complex or *S. prolificans* as airway colonizers is not well accepted and the risk for the development of invasive or disseminated diseases should not be underestimated, especially when the immune system is impaired, as was demonstrated in case 23.^{26,27} Thus, colonized patients with underlying immune diseases should be subjected to regular follow-up evaluations.

As illustrated in our case, CNS involvement represents a devastating complication of pseudallescheriosis/scedosporiosis. The species are frequently reported to exhibit a particular tropism for the CNS, but the mechanisms of the host defense evasion and damage of the blood–brain barrier remain largely unexplained.^{46–50} In this study, CNS manifestations were observed in 41.7% of the AIDS patients with proven IS. Since the rate of dissemination in previously healthy patients, for example after near-drowning, is similar to the data presented here, immunosuppression appears not to be a precondition for CNS manifestations.^{51–53} In our patient, TE was suspected based on typical contrast-enhancing masses in the MRI, neurological symptoms, seropositivity for *Toxoplasma*-specific IgG antibodies, and initial remission of clinical symptoms after administration of antiparasitic therapy. Since similar lesions of different size were the most common finding reported from CNS infections due to members of the *P. boydii* complex,⁵⁴ a computed tomography (CT)-guided needle biopsy at the first time of deterioration would have been required to confirm the diagnosis in our patient.

Mimicking the clinical features of certain other important filamentous fungi, *Pseudallescheria/Scedosporium* species cannot be distinguished from others by the use of histological methods exclusively. Therefore, rapid identification of the infectious organism by molecular methods in parallel to cultures is mandatory and necessary due to the poor response of the species to amphotericin B.^{47,55,56}

Mortality rates after invasive fungal infection are high, especially in patients with disseminated infections. In this study we calculated a mortality rate of 75% for AIDS patients with proven IS. Similar results were reported for *P. boydii* infections in solid organ transplant recipients.⁵⁷ Moreover, the mortality rates differed with respect to the causative agent. Fatality rates of invasive infections due to *S. prolificans* were 100% compared with 75% for infections caused by members of the *P. boydii* complex. In a study reviewing German *S. prolificans* cases, 92% of the patients developed a fatal infection.⁵⁸ The high fatality rate of *S. prolificans* infections may be caused by two facts: (1) conidia contain melanin which has been related to the high affinity to the brain and (2) the species is multidrug-resistant.⁵⁹

The majority of the members of the *P. boydii* complex are resistant to amphotericin B and terbinafine. As *Aspergillus* species are known to be the most common cause of fungal infections, amphotericin B is often used as first-line therapy. It is therefore important to distinguish *Aspergillus* species from *Pseudallescheria/Scedosporium* sp in order to initiate an appropriate antifungal treatment. Miconazole and voriconazole have shown low MIC values against the members of the *P. boydii* complex.^{60,61} Today the intravenous administration of miconazole is limited by its high toxicity and in Germany by its unavailability. Voriconazole is accepted as the gold standard because it has been used successfully in the treatment of CNS infections due to members of the *P. boydii* complex.⁶² The clinical experience with posaconazole against *Pseudallescheria/Scedosporium* sp is limited and this needs further investigation.

In the presented case, voriconazole was combined with caspofungin. New echinocandins lack CNS penetration, an effect also known from amphotericin B. The combination of caspofungin with voriconazole significantly reduced colony counts in lung, liver, kidney and brain tissues in experimental invasive aspergillosis in neutropenic guinea pigs, suggesting a penetration of the drugs into the CNS via the impaired blood–brain barrier.⁶³ For *S. prolificans*, synergistic effects of voriconazole with terbinafine have been observed.^{58,64–66} In our case study, no AIDS patient with *S. prolificans* infection was treated with a combination of terbinafine plus azole, suggesting that this treatment option is not well established.

Multiple studies have confirmed the beneficial effect of additional radical surgical debridement to reduce fungal burden.^{46,47,67} This review demonstrates differences between the mortality rate of patients treated with antifungal drugs alone and those treated with antifungal drugs plus surgery. Similar observations have been reported by Kantarcioglu et al.⁵⁴

In this study, only three of the AIDS patients with proven IS responded to therapy. In all cases the infections remained localized. All patients were infected with members of the *P. boydii* complex. Two non-neutropenic patients underwent radical surgery plus antimycotic treatment. The other survivor did not undergo surgery but was additionally treated with a complex immune-enhancing regime (G-CSF, IFN- γ , GM-CSF). HAART was administered in two patients. The small number of successful clinical outcomes from deep-seated *S. prolificans* infections supported the efficacy of voriconazole plus terbinafine with or without surgery and a supportive immune-enhancing therapy.^{64–66,68}

The introduction of HAART in 1996 has significantly reduced the rates of opportunistic infections. However, most of the proven cases of pseudallescheriosis/scedosporiosis in this review were reported after 1996 (eight vs. four cases).

It has been reported that the receipt of HAART is associated with immune reconstitution disease (IRD) or inflammatory syndrome (IRIS) in approximately 32% of patients.⁶⁹ Due to a lack of information in the reviewed cases we cannot comment on the occurrence of IRIS. For most of the cases, data on the pre- and post-HAART CD4+ cells and HIV-RNA copies were not available.

In our case, an unusual course of the suggested TE could not be excluded. The patient was naïve to ART at the time of diagnosis. She responded well to HAART, resulting in a rapid decrease in the HIV-1 RNA level and a rise in the CD4+ cell count. Thus it remains unclear whether HAART obscured an existing scedosporiosis, or if this infection was acquired secondary to other opportunistic infections like TE.

6. Conclusions

Members of the *P. boydii* complex and *S. prolificans* should be considered in the differential diagnosis as potential causes of

infections in patients with advanced HIV disease. Since cerebral lesions may be caused by various pathogens or by the HIV disease itself, the rapid differentiation between HIV-associated diseases and opportunistic infections is a prerequisite for a successful target-related treatment. Stereotactic CT-guided needle biopsy as early as possible is the most suitable approach to confirm the diagnosis. Serological methods to detect scedosporiosis are not available. Histological examination is necessary to differentiate between colonization and invasive infection, but is unsuitable to identify the fungus. Microbiological investigation, including culture and molecular methods, is indispensable for a correct diagnosis and to initiate an adequate therapy. Radical surgery, wherever applicable, combined with a target-related antimycotic chemotherapy (voriconazole plus terbinafine in the case of *S. prolificans* infections; voriconazole plus caspofungin against members of the *P. boydii* complex) and adjunct immune stimulation advance the clinical outcome.

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